

Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-31 are pending in the application, claims 22-31 withdrawn from consideration by the examiner as being drawn to a non-elected invention, and claims 1, 13, 15 and 19 being the independent claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, applicants respectfully requests that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Support for the amendment to paragraph [0248] of the specification is found in paragraph [0243], last two lines. Said amendment to paragraph [0248] merely corrects a typographical error.

Support for the amendment to claim 1 is found in paragraph [0135]. Support for the amendment to claim 19 can be found *inter alia*, in paragraphs, [0228], [0229], [0240], [0266], [0267], [0268] and [0386], for example.

Priority

The applicants claim the benefit of provisional applications 60/218,244, filed July 14, 2000; 60/ 288,491, filed May 4, 2001; and 60/290,677, filed May 15, 2001, under 35 U.S.C. §119(e).

Information Disclosure Statement

In the action mailed October 17, 2003, the examiner indicated that the Information Disclosure Statement (IDS) filed December 17, 2002 had been considered and an initialed copy of the Form PTO-1449 was attached to the Office Action applicants sincerely thank the examiner. In the interest of avoiding confusion and clarifying the record, applicants provide the following comments.

The examiner stated that the references that were filed with the IDS filed July 18, 2002 were lost in the U.S. Patent and Trademark Office (USPTO) and several attempts to locate them had been unsuccessful. "Rather than return a 16 page Form PTO-1449 completely crossed out," the examiner requested re-submission of the references. Applicants sympathize with the examiner and request that the examiner contact applicants for copies should any be lost again.

The applicants had also filed an IDS electronically on June 3, 2003, and by courier on June 12, 2003, both of which were filed prior to the Office Action mailing date of June 30, 2003. Signed copies of the PTO-1449 forms were not present in the Office Action mailed June 30, 2003.

On August 12, 2003, at the request of the examiner, the applicants re-submitted the documents that had been filed on July 18, 2002, a copy of the IDS previously filed on June 3, 2003, and a copy of the IDS previously filed on June 12, 2003, along with copies

of the return postcards, stamped by the USPTO. Since the references submitted to the USPTO were not considered prior to the mailing of the first Office Action on the Merits, the applicants requested that the Office Action mailed on June 30, 2003 be withdrawn and a new Office Action be issued after the examiner has considered all the references submitted by the applicants. Since the non-consideration of the IDSs was an error on the part of the USPTO, the applicants also requested that a new Shortened Statutory Period be set, based upon the mailing date of the newly-issued Office Action.

In response to the applicants' request, the examiner mailed a communication stating that the Request filed on August 12, 2003 was not responsive because the "Applicant does not address any of the rejections set forth in the previous Office Action at any length." The examiner also asserted that "[t]here is no statutory basis or grounds in the M.P.E.P. upon which such an action should be taken" and that the Office Action was complete as an adequate search was performed to uncover relevant art. The examiner also stated that "[i]n the event that a reference in the IDS must be included in the rejection of a claim or claims in a subsequent Office Action, where the rejection was not necessitated by amendment, a second non-final Office Action will be issued."

Applicants sincerely thank the examiner for his consideration in this regard. The applicants replied with a request to re-issue the Office Action and to reset the time because M.P.E.P. § 609 states that "Once the minimum requirements of 37 C.F.R. 1.97 and 37 C.F.R. 1.98 are met, the examiner has an obligation to consider the information." Therefore, there was a question as to whether the Office Action, which was mailed without consideration of a properly and timely filed IDS was a complete Action.

The Request was filed by the applicants on August 12, 2003, after the applicants contacted the examiner to inform him of the arrival of the filing by courier on August 12. A follow-up telephone call by the applicants to the examiner was made on September 29, 2003, in which the examiner informed the applicants that all the papers have been received as indicated on the USPTO electronic internal database.

Although the applicants maintain that their Request to Vacate the Office Action mailed June 30, 2003 and Request to re-set a new shortened statutory period to respond was proper, in order to preserve the pendency of the present application, a two month Extension of Time, calculated from the June 30, 2003 mailing date of the Office Action is being submitted herewith.

All submitted IDSs have been initialed or otherwise considered by the examiner, as noted in the action dated October 17, 2003. Applicants sincerely thank the examiner in this regard.

Claim Objections

The examiner has objected to claims 1-21 because they are directed to non-elected subject matter, specifically, the recitation of SEQ ID NOS: 1 and 2. The examiner required "appropriate action" to be taken. The applicants request that action be deferred until the claims have been deemed otherwise allowable, so that rejoinder or linking claim practice can be considered, if appropriate.

Rejections under 35 U.S.C. §112

The examiner rejected claims 11 and 12 under 35 U.S.C. § 112, first paragraph as containing subject matter which the examiner alleges was not described in the specification in such a way as to enable one of skill in the art to make and/or use the claimed invention. The examiner stated that ATCC 9058 and NRRL Y-30292 are required to practice the invention.

Assurance is hereby given that the bacterial strain contained in Deposit Number NRRL Y-30292 was deposited under the terms of the Budapest treaty on May 5, 2000. The deposits were made at the United States Department of Agriculture-Agriculture Research Service-National Center for Agriculture Utilization Research (USDA-ARS-NCAUR), 1815 North University Street, Peoria Illinois 61604-3999, and given the accession number of NRRL Y-30292, as disclosed in Paragraph [0222] of the specification. Assurance is also hereby given that the deposited bacterial strains are the same as the bacterial strains described in the specification and that the deposited bacterial strains were in the Applicant's possession at the time of filing (see attached deposit receipt). Finally, assurance is hereby given that all restrictions on the availability to the public of the deposited bacterial strains will be irrevocably removed upon the granting of a patent, subject to 37 C.F.R. § 1.808(b). Withdraw of this rejection is respectfully requested as the Applicant has provided the necessary assurances required by the Examiner for USDA-ARS-NCAUR Deposit Nos. NRRL Y-30292.

The ATCC 9058 cell line is a commercially-available cell line, available through ATCC, as disclosed in Paragraph [0232], applicants have attached a copy of the ATCC on-line Catalog listing for ATCC 9058. Because the strain is commercially available for

sale through ATCC, ATCC 9058 is known and readily available to the public, and thus a deposit is not required to satisfy the enablement requirement as stated in M.P.E.P. § 2402.01.

Applicants have provided the Viability Statement from the Agricultural Research Service Culture Collection and the requisite statement. Applicants therefore believe that the requirements set forth by the examiner have been met and respectfully requests that the rejection be withdrawn.

The examiner has also rejected claims 1-14, 20 and 21 as lacking adequate description that the inventors had possession of the invention at the time the application was filed. The applicants respectfully traverse the rejection. The examiner cited Clyne *et al.*, Identification of autonomously replicating sequence (ARS) elements in eukaryotic cells, *Methods* 13:221-223 (1997), to support his assertion that there is no consensus sequence which would allow one of skill in the art to "identify an ARS element by sequence homology," and that ARS elements isolated from different organisms have been shown to not function as ARS elements. The examiner therefore asserts that the "prior art teaches the unpredictability of predicting ARS functionality by sequence homology, as well as across different organisms." The examiner cites page 225, right column, second and third full paragraphs, in particular.

Clyne *et al.* (1997) describes the identification and comparison of ARS elements in *Schizosaccharomyces pombe* compared with *Saccharomyces cerevisiae*. In the section cited by the examiner (*See* page 225), the authors were merely stating activity found using the yeast transformation assay described in the article, and sequence similarities were reviewed in detail. Additionally, Clyne *et al.* (1997) on page 224, right-hand

column, last paragraph states that "In practice, by using a limited amount of plasmid DNA and scoring colony formation after only a few days of incubation, ARS elements can be readily identified on the basis of transformation frequency alone." As the document cited by the examiner discusses two species, *Schizosaccharomyces pombe* and *Saccharomyces cerevisiae*, besides the *Candida famata* claimed by the applicants, as also having ARS activity, the applicants assert that there is sufficient disclosure for one of skill in the art to determine that the inventors had possession of the claimed genus at the time of filing the application.

Regarding the rejection of claims 1, 3 and 6, the applicants have amended claim 1 to include the function of the ARS in yeast. As the sequence of SEQ ID NO:3, recited in claim 1, provides a structure to the claimed sequence, the applicants have provided a "disclosure of relevant identifying characteristics coupled with a known or disclosed correlation between structure and function" as required by the examiner in paragraph 2, page 7 of Paper No. 17.

Regarding the rejection of claims 2, 4, 5, 7-12, 14, 20 and 21, applicants respectfully submit that the claims do not lack written description, as the structure, SEQ ID NO:3, as recited in claim 2, is a limited genus, defined by any member containing SEQ ID NO: 3. As claim 2 is limited to a nucleic acid comprising SEQ ID NO: 3, the claim has full written description support, as discussed in the "Interim Written Description Guidelines" (herein "the Guidelines") in Example 8, pages 33-35 of the Guidelines. Using the analysis in the Guidelines, a review of the full content of the specification indicates SEQ ID NO:3 is essential to the operation and function of the invention as claimed herein. The specification indicates that SEQ ID NO: 3 is a *Candida*

famata VKM Y-9 ARS element (CfARS). The claim is drawn to a nucleic acid comprising a yeast ARS element. The claimed nucleic acid does not read on a genomic sequence because a full length yeast ARS would not be expected to contain introns and regulatory elements that are found in genomic DNA. The claims read on the claimed ARS element in any construct or with additional nucleic acid residues placed with the ARS. As the examiner has not applied any art against SEQ ID NO: 3, then the polynucleotide is a novel and unobvious sequence. There is a single species explicitly disclosed, a polynucleotide molecule consisting of SEQ ID NO: 3 that is within the scope of the claimed genus. There is an actual reduction to practice of the disclosed species (*See the Examples*). One of skill in the art can readily envisage nucleic acid sequences which include SEQ ID NO: 3, because e.g. SEQ ID NO: 3 can be readily embedded in known vectors. Although there may be substantial variability among the species of DNAs encompassed within the scope of the claim because SEQ ID NO: 3 may be combined with sequences known in the art, e.g. expression vectors, the necessary common attribute is the ARS element of SEQ ID NO: 3. Weighing all factors including (1) that the full length ARS element, SEQ ID NO: 3 is disclosed and (2) that any substantial variability within the genus arises due to addition of elements that may or may not be part of the inventors' particular contribution, taken in view of the level of knowledge and skill in the art, one skilled in the art would recognize from the disclosure that the applicants were in possession of the genus of polynucleotides that comprise SEQ ID NO: 3.

The applicants believe they have addressed the concerns of the examiner and request that the rejection be withdrawn.

The examiner has also rejected claims 15-18 under 35 U.S.C. § 112, first paragraph, because the examiner stated that "the specification, while being enabling for a method for electroporating *Candida famata*, does not reasonably provide enablement for any yeast strain." The applicants respectfully traverse the rejection.

The basis for the rejection, as the examiner has set forth through a "Wands Analysis" for the invention, is that the field strength of 8-15 kV/cm has not been shown by the applicants to be applicable to all yeast strains. The examiner has cited Raymond *et al.* (U.S. Patent No. 5,854,039) as being representative of the state of the art. The '039 patent teaches 2.54 - 4.5 kV/cm and teaches away from the range claimed by applicants, according to the examiner.

The applicants respectfully disagree. The '039 patent is but one of a body of references regarding field strength. The '039 patent merely states one set of conditions that was optimized for Raymond's own system. The '039 patent does not teach that higher voltages are detrimental or renders the present invention non-enabled for the full scope of the invention. Rather, the '039 patent states that other parameters, such as resistance are also important. The '039 patent discloses resistance settings of 200, 600 or "infinite" ohms of resistance (see column 16), and the importance of capacitance as well (measured in Faradays (F)). The resistance in the present invention was 13-720 ohms (Ω) (claim 16) or more specifically, 129 ohms (claim 17). Becker and Guarente (*Meth. Enzymol.* 194:182-187, (1991); Document **AR1** on the IDS filed July 18, 2002) reported the use of a field strength of 7.5 kV/cm for use in *Saccharomyces cerevisiae*. Faber *et al.* (*Curr. Genetics* 25:305-310, (1994); Document **AT3** on the IDS filed July 18, 2002) reported that the "[p]ulse field strength can be varied between 0 and 2.5 kV (0-12.5

kV/cm using 2-mm cuvets)" and the resistance may be adjusted from 13 ohms to 1048 ohms, at a fixed capacitance of 50 μ F (page 306, left column). Faber *et al.* used *Hansenula polymorpha* for electroporation. Pla *et al.* (*Gene* 165:115-120, (1995); Document **AR9** on the IDS filed July 18, 2002) used 2.4 kV at 5 msec, 129 Ω , and a 0.2 cm cuvette length (0.2 cm \approx 2 mm) for use in *Candida albicans* transformation (See page 119, left column). Pla *et al.* did not disclose the calculated field strength. Scorer *et al.* (*Bio/Technology* 12:181-184, (1994); Document **AS10** on the IDS filed July 18, 2002) disclosed transformation of *Pichia pastoris* using 1.5 kV, 25 μ F, and 400 Ω , with no field strength mentioned (See page 183, right column). Sreekrishna and Kropp (*Nonconventional Yeasts in Biotechnology, A Handbook*; Wolf, K, ed., Springer-Verlag, New York, (1996); Document **AR13** of the IDS filed July 18, 2002) disclosed the use of 25 μ F, 2.5 kV and 200-600 Ω (400 Ω recommended) for use in *Pichia pastoris*, (See page 226), based upon the reference by Becker and Guarente (*Meth. Enzymol.* (1991)). Additionally, Kasüske *et al.* (*Yeast* 8:691-697, (1992); Document **AR5** on the IDS filed June 18, 2002) discloses a range of 2.4 kV/cm and 12.5 kV/cm in Figures 2 and 3. Kasüske *et al.* teaches a procedure, also based on Becker and Guarente (*Meth. Enzymol.* (1991)), to determine electroporation field strength (100 Ohm, capacitance of 25 μ F or 40 μ F, 0.2 cm cuvettes) on transformation efficiency of *Candida maltosa* and cell survival (See pages 693 and 694). It is clear, that given the disclosure of the invention and the prior art, one of skill in the art would be able to transform many commonly-used yeast and fungal strains in the range claimed by the applicants.

The applicants respectfully submit that the invention as claimed in claims 15-18 is enabled over a wide range of well-known and divergent species (*Saccharomyces*

cerevisiae, *Hansenula polymorpha*, *Pichia pastoris*, *Candida maltosa* and *Candida albicans*, for example), and that one of skill in the art, using the applicants' specification as guidance, could reasonably predict "that their cells would respond to the particular field strength of 8-15 kV/cm," as stated by the examiner on page 9 of the Office Action. Also, given the guidance of suggested field-strength ranges in both the disclosure and the known art, one of skill in the art would have been able to practice the invention without undue experimentation, given the guidance and working examples provided in the specification. The applicants therefore request withdrawal of the rejection.

Rejections under 35 U.S.C. §102

The examiner has rejected claim 19 as being anticipated by Raymond *et al.*, U.S. Patent No. 5,854,039. The examiner stated that the '039 patent taught a "method of transforming the yeast *Pichia methanolica* using a cell suspension of said yeast cells together with DNA molecules, such as expression cassettes that contain promoter and terminator elements and a gene of interest. The transformation method involves electroporation of the cells, which have been washed in an electroporation buffer which comprises sucrose." [citations omitted by applicants]

The applicants respectfully traverse the rejection for the following reasons:
Claim 19 is drawn to a method of transformation of yeast using electroporation of said yeast cells in a suspension containing sucrose. Claim 19 as amended, requires that sucrose is present in the electroporation buffer to contain 0.3 M to 1.0 M sucrose concentration. The '039 patent only discloses a buffer containing 0.27 M sucrose in the

electroporation buffer (col. 7, lines 21-23 and col. 13, line 15), and thus does not anticipate the claimed invention.

The applicants believe they have addressed the concerns of the examiner and request that the rejection be withdrawn.

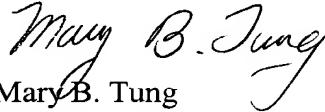
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully requests that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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